Retrophin Announces New Data Supporting Further Clinical Development of RE-024 for PKAN at the 2016 American College of Medical Genetics and Genomics Annual Clinical Genetics Meeting

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SAN DIEGO, March 09, 2016 (GLOBE NEWSWIRE) -- Retrophin, Inc. (NASDAQ:RTRX) today announced new data supporting further clinical development of RE-024, the Company's novel investigational replacement therapy for pantothenate kinase-associated neurodegeneration (PKAN), a rare and life-threatening genetic disorder with no approved treatments. Key findings suggest RE-024 was safe and well-tolerated in healthy volunteers and showed sustained clinical benefit over a 12-month period in a single PKAN patient who received the compound as part of physician-initiated treatment. In addition, preclinical data describe the development of the first human cellular model of PKAN, as well as animal studies supporting the proposed mechanism of action of RE-024 and its potential to distribute to the brain in humans.

These and other data from four posters will be presented at the 2016 American College of Medical Genetics and Genomics (ACMG) Annual Clinical Genetics Meeting on March 10 and 11 in Tampa, FL. Today, e-versions of the posters were made available to registered attendees.

"These findings provide important foundational evidence, including initial insights into the pharmacokinetic profile and mechanism of action of RE-024, which have already helped shape the future of our clinical development program for this novel compound," said Alvin Shih, M.D., executive vice president and head of research & development for Retrophin. "We look forward to applying this knowledge further as we aim to address an important unmet medical need for patients living with this progressively debilitating genetic disorder."

Healthy Volunteer Phase 1 Study (Poster 670, Friday, March 11)

In a Phase 1 single ascending dose study of 40 healthy adult volunteers, RE-024 was found to be safe and well-tolerated. The double-blind, placebo-controlled study evaluated five oral dose levels of the compound (75, 225, 450, 900 and 1800 mg). No serious adverse events were reported and no patients dropped out of the study. All of the 21 treatment-emergent adverse events (TEAEs) reported were mild. The rate of TEAEs associated with RE-024 were comparable to placebo (36.7 percent or 11/30 and 30 percent or 3/10, respectively).

Across all doses, 12 of the TEAEs were thought to be possibly related to treatment, with the majority either directly (eight) or indirectly (two) associated with taste. The two remaining TEAEs seen were diarrhea and hiccups.

Further, the compound was rapidly absorbed with exposures consistent with increasing dose levels and a time to maximal concentration observed between 0.33 and 1.42 hours. Mean increases in blood exposure were linear through 450 mg and became slightly less than dose proportional between 450 mg and 1800 mg. Based on the pharmacokinetic findings to date, RE-024 may need to be administered in multiple daily doses to achieve adequate coverage.

Open Label Treatment with RE-024 (Poster 659, Thursday, March 10)

Findings from a case report describe physician-initiated treatment of a 35-year-old male PKAN patient with RE-024 who initially presented with gait instability at 22 years of age, followed by progressive deterioration that resulted in being wheelchair bound by the age of 34. The treating physician reported that, under RE-024 treatment, the patient experienced persistent improvement in symptoms, including ability to walk, followed by stabilization during the 12-month observation period.

RE-024 was initiated at a low dose and gradually increased over one week to 240 mg daily (3 mg/kg/day), administered orally as 80 mg three times per day. RE-024 entered the blood stream rapidly, and the pharmacokinetic profile was comparable to results reported from the Phase 1 study in healthy adult volunteers.

RE-024 was well-tolerated in the patient. The individual experienced transient nausea and mild elevation of transaminases to approximately two-to-three times the upper limit of normal, which resolved after discontinuing treatment and did not recur following re-challenge at a lower dose one week later. Further, these adverse events did not recur after subsequent dose increases.

The patient showed meaningful improvement over the first three months in all clinical parameters. Notable improvements were a greater than 30 percent reduction in Unified Parkinson's Disease Rating Scale Parts II and III scores assessing activities of daily living and a neurological motor exam, respectively, and a 25 percent improvement in gait speed, with regained ability to walk independently for short distances. These changes were followed by approximately nine months of stabilization at the improved levels, suggesting the potential durability of sustained treatment with RE-024 in this otherwise progressive disease. The treating physician noted that this degree of improvement in motor function is not reflective of the natural history of PKAN, however, in open treatment, placebo response cannot be ruled out. The physician also concluded that the therapeutic potential of RE-024 should be evaluated in controlled studies of PKAN patients.

Human Neuroblastoma Model of PKAN (Poster 668, Friday, March 11)

Results from preclinical studies describe the development of a human neuroblastoma model of PKAN that has been used as a tool for screening and characterizing drug candidates designed to restore coenzyme A (CoA) levels in a PKAN-deficient setting. This is the first human cellular model in which the silencing of *PANK2* by shRNA leads to decreased CoA levels, as well as decreased tubulin and histone acetylation. In the shRNA *PANK2*-silenced human neuroblastoma cells, administration of RE-024 led to restored CoA levels, as well as histone and tubulin acetylation.

Mechanism of Action and Efficacy in Preclinical Models (Poster 669, Thursday, March 10)

In additional experiments, RE-024 delivered orally to mice and rats resulted in incorporation of RE-024-derived phosphopantothenate (PPA) into CoA

in the liver. Oral doses of RE-024 in mice and rats did not result in detectable RE-024 in brain dialysate, likely due to the short half-life in blood (less than five minutes). Concentrations of pantothenate (PA) and PPA after oral dosing in mice were measurable at levels of 161.5 and 64.8 nM respectively. Intrastriatal administration of RE-024 in mice demonstrated incorporation of RE-024-derived PPA into brain CoA. These data indicate that if RE-024 reaches the brain, it is expected to deliver PPA intracellularly to be incorporated in CoA.

After a 700 mg/kg oral dose in monkeys, RE-024 concentrations reached 18700.0 nM in whole blood, and reached 6543.0 nM in brain dialysate within 30 minutes of dosing, with concentrations of PA and PPA reaching 749.8 and 858.6 nM, respectively. The maximum concentration of RE-024 in brain dialysate was approximately 30 percent of the whole blood concentration. The whole blood half-life in monkeys was longer than in mice, allowing for distribution to the brain. The similar half-life between monkeys and humans, as shown in the Phase 1 study, is supportive of RE-024 distribution to the brain in humans.

About Pantothenate Kinase-Associated Neurodegeneration (PKAN)

Pantothenate kinase-associated neurodegeneration, or PKAN, is a rare, genetic, and life-threatening neurological disorder characterized by a host of progressively debilitating symptoms that typically begin in early childhood. People suffering from PKAN may experience movement disorders such as dystonia (sustained muscle contraction leading to abnormal posture), rigidity, dysphagia (problems swallowing), twisting and writhing, and tremors, as well as visual impairment. There are no approved treatment options for PKAN and current therapeutic strategies are limited to palliative care. PKAN is estimated to affect up to 5,000 people worldwide.

PKAN is caused by a mutation in the *PANK2* gene, which encodes a critical protein that phosphorylates vitamin B5 (pantothenate) to phosphopantothenate. The disruption of this metabolic pathway ultimately leads to decreased levels of coenzyme A (CoA), which plays an important role in many cellular functions.

About RE-024

RE-024 is a novel small molecule in Phase 1 clinical development that has the potential to be the first approved replacement therapy targeting the underlying cause of PKAN. Preclinical findings suggest RE-024 has the ability to restore CoA levels and to distribute to the brain. Retrophin is preparing to conduct an efficacy trial of RE-024 in patients with PKAN that is expected to initiate in 2016.

In 2015, the U.S. Food and Drug Administration granted orphan drug designation to RE-024 for the treatment of PKAN, as well as Fast Track status which is designed to facilitate the development and expedite the review of medicines to treat serious conditions with unmet medical needs in order to reach patients earlier. In 2016, the European Commission granted orphan drug designation to RE-024, which is granted to a medicinal product intended to treat a life-threatening or chronically-debilitating rare disease with no approved treatment option.

About Retrophin

Retrophin is a fully-integrated biopharmaceutical company dedicated to delivering life-changing therapies to people living with rare diseases who have few, if any, treatment options. The Company's approach centers on its pipeline featuring clinical-stage assets targeting rare diseases with no approved treatment options, including sparsentan for focal segmental glomerulosclerosis (FSGS), a disorder characterized by progressive scarring of the kidney often leading to end-stage renal disease, and RE-024 for pantothenate kinase-associated neurodegeneration (PKAN), a life-threatening neurological disorder that typically begins in early childhood. Research exploring the potential of early-stage assets, including RE-034, in several rare diseases is also underway. Retrophin's R&D efforts are supported by revenues from the Company's marketed products Chenodal®, Cholbam® and Thiola®.

Retrophin.com

Forward-Looking Statements

This press release contains "forward-looking statements" as that term is defined in the Private Securities Litigation Reform Act of 1995. In addition, expressions of our strategies, intentions or plans are also forward-looking statements. Such forward-looking statements are based on current expectations and involve inherent risks and uncertainties, including factors that could delay, divert or change any of them, and could cause actual outcomes and results to differ materially from current expectations. No forward-looking statement can be guaranteed. Among the factors that could cause actual results to differ materially from those indicated in the forward-looking statements are risks and uncertainties associated with the Company's business and finances in general, as well as risks and uncertainties associated with the Company's research preclinical and clinical stage pipeline. Specifically, the risks and uncertainties the Company faces with respect to its RE-024 program include risk that RE-024 will not progress to Phase 2 or later-stage clinical trials for safety, regulatory or other reasons; risk associated with enrollment of clinical trials for rare diseases; risk that the company's later stage RE-024 clinical studies will fail to demonstrate that RE-024 is safe and effective. You are cautioned not to place undue reliance on these forward-looking statements as there are important factors that could cause actual results to differ materially from those in forward-looking statements, many of which are beyond our control. The Company undertakes no obligation to publicly update forward-looking statement, whether as a result of new information, future events, or otherwise. Investors are referred to the full discussion of risks and uncertainties as included in the Company's filings with the Securities and Exchange Commission.

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